

Themed Issue: Drug-Induced Hypersensitivity Reactions

Guest Editor - Craig Svensson

Commentary: Drug Hypersensitivity — Where Do We Stand?

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As the cost of developing new therapeutic agents continues to escalate, the economic effect of drug failure at any stage during development has also increased. While biopharmaceutical/pharmacokinetic problems used to represent one of the most common causes of failure in drug development, current evidence indicates that once efficacy is demonstrated, the primary cause of drug failure arises from drug toxicity. Indeed, the development of toxicity undetected during clinical trials is the primary cause of drug removal from the market.

Among the various forms of drug toxicity, the development of hypersensitivity reactions is particularly problematic. Occurring in a very small portion of the population exposed to a drug, these reactions are associated with significant morbidity and mortality. At present, there are no validated means by which investigators are able to identify those agents most likely to provoke a hypersensitivity reaction or identify which patients are at unacceptably high risk (such that therapy with a specific drug should be avoided).

Recognizing the effect of hypersensitivity reactions associated with drug therapy, both in terms of economic and patient health considerations, understanding the mechanism of these reactions is of obvious importance. Furthermore, such reactions may provide significant tools to obtain novel insight into the underlying pathophysiology of numerous immune-mediated diseases. Hence, much fruit may be borne from the elucidation of mechanism(s) of drug hypersensitivity reactions.

In this themed issue, we have assembled a group of reviews by investigators whose research focuses on elucidating the mechanism of drug-induced hypersensitivity reactions. These reviews present a concise and critical analysis of our current knowledge in this important class of drug toxicity.

The article by Jack Uetrecht provides an insightful analysis of animal models for studying drug hypersensitivity reactions.¹ For the past decade or more, the Uetrecht lab has pursued several potential animal models to provide a platform by which to probe the mechanism of these reactions. Of the models developed to date, penicillamine-induced autoimmunity in the Brown Norway rat and nevirapine-induced skin rash in the rat provide the greatest mechanistic insight. Both models provide evidence that these reactions are T-cell mediated, as the adoptive transfer experiments described clearly demonstrate. The strain-dependent

response to penicillamine should prove useful for probing the genetic determinants of this reaction. Furthermore, while hypersensitivity reactions are often stated to be dose-independent, the nevirapine-induced skin rash model provides a strong basis by which to refute this notion.

Also discussed in this review are animal models that may be considered for screening compounds for their potential to provoke hypersensitivity reactions. Though widely used, the popliteal lymph node assay in its present form appears to possess poor predictive capacity for identifying agents likely to induce hypersensitivity reactions after systemic administration. The reporter antigen lymph node assay is a variant of the popliteal lymph node assay that may prove more useful but requires considerably more evaluation before any assessment can be made.

In short, there currently are no good screening methods to identify compounds during development that have the potential for provoking hypersensitivity reactions. While some scientists have promoted the use of covalent binding assessments as a means of identifying compounds with significant potential to cause toxicity, one must ask what our therapeutic armamentarium would look like at present if we eliminated all drugs currently in use that exhibit significant covalent binding. At a time when the pipeline for drug development has few compounds of promise, can we afford the false positives that will result from this approach?

In another article in this series, Holt and Ju² describe the complex mechanisms that appear to govern the development of drug-induced liver injury. In their review, the authors describe evidence that drug-induced liver injury involves elements of both the innate and adaptive immune systems. As described by Holt and Ju, even agents that initiate liver injury through a direct hepatotoxic effect (eg, acetaminophen) may stimulate an immune response. Indeed, for such drugs, the provocation of an immuno-inflammatory response may be what differentiates mild liver injury from severe liver injury. Using acetaminophen as an example, these authors describe the complex interplay between drug-induced cell stress or death and the innate immune system. This mechanistic insight may provide important clues to the means by which measures for covalent binding may be refined to predict the potential for adverse drug reactions (eg, cell-based screening assays that assess release of mediators of the innate immune system).

Holt and Ju² also describe evidence that the adaptive immune system mediates liver injury for some drugs. Mechanistic investigation into these immune-mediated reactions has been hampered by the absence of a good animal model, as well as the logistic and ethical constraints of studying human subjects with such reactions. At present, our best hope for gaining such knowledge may rest in the development of multi-center investigations, such as the Drug-Induced Liver Injury Network that is described. As drug-induced hepatotoxicity appears to be the most frequent reason for drug withdrawal and is among the most common causes of liver failure, the need for greater mechanistic insight into these reactions is compelling.

In this themed issue, Sanjoy Roychowdhury and I³ assess our current understanding of the mechanism for cutaneous drug reactions. As the most common of the drug hypersensitivity manifestations, even when mild in nature, these reactions often result in the removal of effective drug therapy from patients' therapeutic regimen. We believe that the immune events that occur after application of contact sensitizing agents to the skin provides important insight into the mechanisms by which systemically administered drugs may provoke a skin eruption. In this article, we discuss important mediators of the immune response that may play a critical role in the development of cutaneous drug reactions.

It is apparent that a key question regarding the mechanism of these reactions is the importance of events occurring in the skin. While we describe evidence that suggests events initiated in the skin are necessary to provoke an immune response in the skin, these are inferred from studies of contact hypersensitivity and have yet to be clearly demonstrated for systemically administered drug. Such evidence is a necessary next step in further elucidating the mechanism of these reactions. It will also be critical for the development of preclinical screening tests (eg, the ability to provoke dendritic cell migration) to predict drugs likely to be associated with drug eruptions. One important, yet unexplored, question is what differentiates patients who experience mild skin eruptions from those that exhibit serious cutaneous reactions? Arguably, it is these latter reactions with which we should be most concerned, even though their frequency is lower than the former.

Kevin Park, whose laboratory has been at the forefront of advances in understanding the relationship between the formation of reactive metabolites and drug toxicity, joins with colleagues in Liverpool to provide a review of the role bioactivation in the provocation of drug hypersensitivity reactions. Sanderson, Naisbitt, and Park⁴ specifically focus on the means by which the formation of reactive metabolites activates the immune system. Using sulfamethoxazole as a model compound, these authors provide a concise and critical summary of the role of covalent binding by reactive metabolites in the stimulation of T cells. As described by

these authors, such metabolites may also provoke the release of danger signals that activate immune cells. This interplay between the formation of haptenated proteins and the release of key immune mediators provides interesting avenues of investigation for therapeutic management of these reactions and the development of in vitro screening methods.

Since reactive metabolites are inherently unstable, these authors discuss the potential importance of the site of bioactivation in the initiation of immune responses to drugs. As noted by these authors, the potential for extrahepatic bioactivation has been demonstrated through various means, yet its role in target organ toxicity remains to be determined. While recent work in the development of animal models of tissue-specific expression or knockout of drug metabolizing enzymes provides a powerful tool for assessing the role of extrahepatic metabolism, the inability to provoke these reactions in animals hinders our ability to take advantage of such models for investigations of hypersensitivity reactions. Hence, the importance of extrahepatic generation of reactive metabolites in drug-induced hypersensitivity reactions remains unclear.

The role of genetics has been an important focus of studies seeking to identify predisposing factors for drug-induced hypersensitivity. Munir Pirmohamed⁵ provides an excellent assessment of our current evidence for the role of genetic variants as risk factors for these reactions. Through a cogent assessment of current literature, Pirmohamed shows that the initial predictions that genetic variation in drug metabolizing enzymes would prove to be a major source of predisposition to hypersensitivity reactions have not been realized. In contrast, recent work has provided strong evidence for the importance of genetic variants in key immune molecules in predisposing patients to drug-induced hypersensitivity. The author discusses the implication of recent observations that indicate a strong association between hypersensitivity reactions to abacavir and carbamazepine with specific haplotypes of HLA. These data provide important evidence that such reactions are immune mediated.

Often absent from discussions of predisposition to these reactions is the cost-effectiveness of predictive tests for use in the clinical setting. From investigations by his own group and that of others, Pirmohamed places this critical issue in perspective for abacavir genotype associations. As more such associations are identified, cost assessments will be crucial in considerations of their adoption into clinical therapy. Of further, but unexplored, consideration are ethical imperatives associated with such tests. Is it ethical to fail to use a test that may prevent a small number of patients from experiencing a life-threatening reaction because it is not cost-effective from an economic perspective? As further genetic associations are identified with drug hypersensitivity reactions, these ethical considerations must be an important component in the assessment of test adoption.

The interaction between genes and environment is undoubtedly a critical consideration in evaluating the risk of developing hypersensitivity reactions. As described in this article, strong evidence for the role of viral infection as a predisposing factor for hypersensitivity reactions exists for several drugs. This relatively unexplored area merits more intensive investigation and may explain why some patients with a history of hypersensitivity do not exhibit a reaction upon re-exposure to the offending agent.

Finally, Gerber and Pichler⁶ review growing evidence that the classic hapten hypothesis may not provide an adequate explanation for some immunological responses to drugs. The Pichler group has been at the forefront of providing evidence that parent drug associated with the major histocompatibility complex (MHC) (HLA) complex in a noncovalent manner is able to stimulate T cells. As described by Gerber and Pichler, this work has caused a reconsideration of long-accepted concepts in the response of the immune system to xenobiotics. It is important to recognize that the Pichler group has not argued that the hapten-hypothesis is invalid, but (as well presented in this review) that it is unable to explain all observations associated with drug hypersensitivity.

A critical question remaining unanswered in this modality of T-cell stimulation is whether initial sensitization could occur in the context of noncovalent association. As T-cell-mediated responses appear to be initiated as a consequence of clonal expansion of such cells in lymph nodes, how would migrating dendritic cells “carry” drug associated with such cells in a noncovalent manner? Indeed, in the absence of antigen uptake (ie, haptenated proteins) would there be sufficient signals for dendritic cell migration and activation? This is perhaps where the classic hapten hypothesis and the p-i concept (pharmacological-interaction) interact. As suggested by these authors, it may be that drugs are

inducing a secondary response via cross-reactivity with immune cells previously primed to an unrelated antigen. Further work is needed to validate this hypothesis, but it appears conceptually sound. Ongoing work in cells expressing cloned T-cell receptors promise to provide important insight into these questions. Indeed, it is not unreasonable to postulate that understanding the structural determinants for T-cell receptor activation in this context may provide the basis for the development of in vitro assessments of patient susceptibility to specific drugs known to be associated with hypersensitivity reactions.

It is hoped that this collection of reviews provides readers with a coherent and comprehensive assessment of the current state of our knowledge regarding the mechanisms of drug hypersensitivity. Knowledge gained over the past decade provides the basis for anticipation that key advances in this arena will make a significant impact on the prediction and management of drug hypersensitivity reactions.

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